

THE PROPHYLACTIC USE OF TETANUS ANTITOXIN.¹

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IN 1890 Behring and Kitasato published in the *Deutsche medizinische Wochenschrift* an article entitled "Ueber das Zustandekommen der Diphtheria-Immunität und der Tetanus-Immunität bei Thieren." In this paper for the first time are laid down the principles which underlie the elaboration and properties of tetanus antitoxin. The authors showed that when rabbits or mice had been appropriately treated with tetanus toxin of reduced virulence they were not only able to withstand inoculation by fully virulent tetanus bacilli, but were also protected against the injection of twenty times the minimal lethal dose of tetanus toxin. In short, these animals had been vaccinated by means of tetanus toxin and had thereby acquired an active immunity. This immunity was found to rest largely in the blood serum, which when separated from the blood of these animals and injected into other animals was able to afford protection against subsequent injections of otherwise fatal doses of tetanus toxin or the inoculation of virulent tetanus cultures. One produced in these latter animals, by the injection of this antitoxic serum, a passive or so-called prophylactic immunity against tetanus. The evidence that this serum also possesses certain curative possibilities, and can be used as a therapeutic remedy, with more or less success against outbreak tetanus in man and animals, will be discussed in a future paper. At present our attention must be confined not to the cure but to the prevention of tetanus, not to the therapeutic but to the prophylactic properties of tetanus antitoxin.

On the laboratory side the facts in regard to the protective properties of tetanus antitoxin established by Kitasato and Behring were rapidly confirmed and amplified by other workers, among these Tizzoni, Roux and Vaillard, Donitz and Tavel. Thus, Roux and Vaillard stated in 1893 that antitetanic serum injected, even in extremely small doses, before the tetanus toxin would surely prevent tetanus, and Tavel, in 1895, designated the prophylactic inoculation of the serum as "absolutely certain." In fact, so positive and sure did this protective action of antitoxin appear that for nearly a decade clinical and laboratory efforts were almost entirely directed toward establishing the value of tetanus antitoxin as a curative agent and little or no attention was devoted to its acknowledged prophylactic value.

Nocard was the first to emphasize by practical application the usefulness of the serum as a protection against tetanus. The frequency of this disease following operations on horses led him early to test the effect of systematic prophylactic inoculation in all injured or operated animals, and in 1897 he reported some of his results to the French Académie de Médecine. Of 3500 horses inoculated in the preceding twenty-two months the results were known in 2727. Not one of these 2727 horses developed tetanus in spite of the fact that they came from a quarter of Paris where this disease was very prevalent and where in the same length of time 259 cases of tetanus occurred among non-inoculated animals. Of the 2727 horses, 2300 were inoculated immediately following the operation (in most cases castration). Similar results have been reported by other veterinary surgeons, for example, Bigot, Smidt, Rickmann, and Mullotte.

Naudrin, in whose practice, during a course of five years, 8 colts had died of tetanus infection of navel, operativ wounds, etc., in the succeeding six years had used preventive injections of antitoxin with entire success. Pecus, after only a single protective inoculation in 1500 horses among which 500 had been wounded by stepping on nails, had not seen a single case of tetanus. The Höelst Farlwerke relate that in the bacteriological division, in which yearly about 300 horses and mules are used to produce serums, since the establishment of systematic and regular prophylactic injections of antitetanic serum, not one case of spontaneous tetanus has been observed. In the United States, McFarland (1903) reported that in a stable of 800 horses the mortality from tetanus became so high that strenuous sanitary measures were demanded. Accordingly the stalls and horses were thoroughly cleansed and disinfected, but without success. The decision to move into entirely new quarters was made when the use of tetanus antitoxin was suggested. The results were most gratifying. The prophylactic injections were first used systematically in 1899, and since that time the yearly mortality from tetanus had remained below 1 per cent. Munich, having successfully protected 48 injured and operated animals, three years later added 150 cases with only one failure. Vaillard, in a report of statistics collected from ten veterinary surgeons, stated that among 13,124 animals which had been injected with antitetanic serum, after either a surgical operation or an injury, not one had developed tetanus. These results led him to recommend strongly that this method should receive more consideration in human medicine.

Before this time, however, the value of prophylaxis against tetanus in human beings was being recognized. As early as 1899 v. Rosthorn reported that in his obstetric service in Prag he was disturbed by an epidemic of tetanus. Almost every woman who was delivered became infected and died. No source could be found,

and in spite of "most thorough disinfection," with closure of the clinic at two different periods, no relief was obtained until antitoxin injections were systematically used. "We possess in tetanus antitoxin an agent that not only is able to permit a favorable prognosis in the ordinary uncomplicated case of traumatic tetanus, but also can prevent the further spread of an epidemic of puerperal tetanus, which disease may occur even after the most careful asepsis." (v. Rosthorn.)

The following year (1900) v. Leyden and Blumenthal, impressed by Nocard's results as well as those of their own experiments, wrote: "The employment of prophylactic antitetanic serum is to be recommended for all suspicious cases of abortion or of injuries, especially those in which dirt has entered."

Herhold, in 1901, described four cases of tetanus which occurred within a period of eight weeks in a field hospital in China. After systematic antitoxin injections in all cases with unclean wounds no further tetanus appeared. Schwartz in the same year declared that his hospital in Cochin, China, had become a regular "breeding-place" for tetanus until antitoxin finally ended the epidemic.

At the Fifteenth French Congress of Surgery, in 1902, there were especially favorable results reported from the systematic prophylactic treatment of all suspicious wounds. Championnière, when a case of puerperal tetanus on his service had been shortly followed by two other cases which developed in spite of every precaution, on the advice of Roux administered prophylactic antitoxin to all subsequent confinement cases, and for the past four years had encountered no further trouble from tetanus. Raboul, Bazy, Guinard, and Schwartz declared that for years routine prophylactic injections of serum in all cases with unclean wounds had been a rule on their services, and in no case so treated had tetanus developed. The first three surgeons each observed a case of tetanus in which the prophylactic injection had been accidentally omitted. Vallas went so far as to insist that for a physician not to give prophylactic antitoxin to all cases with dirty wounds was a failure in correct treatment. He believed the universal practice of this method would cause tetanus to disappear.

In this year also Barthélemy, from the results of experiments on animals, strongly recommended the intravenous administration of antitoxin for prophylactic purposes, and predicted that by this method many lives might be saved even when the antitoxin was administered late in the incubation period.

Calmette, in 1903, proposed a new method of using antitoxin on wounds, namely, as a dry powder. In experiments on tetanus-infected wounds in guinea-pigs he was able to prevent death by using antitoxin in this manner as late as seven hours after infection. As a result of these experiments and his experiences on the west coast of Africa, where wounds were generally unclean and tetanus

extremely prevalent, he advised in all cases of injuries prophylactic inoculation either by subcutaneous injection of 10 c.c. fluid serum or by the application of dry antitoxin on the wound. He especially recommended the sprinkling of powdered antitoxin on the umbilical cord stumps of infants for combating tetanus neonatorum. That in such cases the method has real value was shown by Letulle, who used it extensively in Indo-China, where one-fifth of the newborn babies died of tetanus. After the systematic use of the antitoxin powder tetanus neonatorum practically disappeared. Norris in this same year, from a study of 57 cases, concluded that all those with wounds in which there might be a possibility of tetanus infection should receive prophylactic injections of antitoxin.

In 1905 Suter gave a very thorough review of this subject with statistics from Julliard's surgical clinic in the Geneva Hospital, where, since 1896, more than 700 patients with fresh wounds had received prophylactic injections of tetanus antitoxin (10 c.c.). Two patients in whom the treatment was accidentally omitted developed tetanus and died, while only one of the 700 treated cases showed any symptoms of the disease and no bad results followed in consequence of the serum injections, except for a light urticarial eruption in two cases.

At the Thirty-fifth Congress of the German Surgical Association, held in Berlin in 1906, the subject of tetanus prophylaxis was vigorously discussed. The opinions there expressed were decidedly varying; for example, Zoege v. Mantuffel, Wreden, Körte, and others opposed as useless the administration of tetanus antitoxic serum, while Freiderick, Hecker, Kocher, Pochhammer, and Uhlenhuth expressed their confidence in the method. Kocher declared: "I should strongly resent it and call him to account if a doctor, in treating a relative of mine who had received a wound which was infected with street dirt, did not administer a prophylactic injection of tetanus antitoxin." Uhlenhuth, after reporting on the frequency of the tetanus spores in the clothing of soldiers, added that all soldiers of the II Army Corps whose wounds were complicated by earth, filth, or pieces of clothing were ordered to receive an immunizing dose of antitetanic serum.

Lotheissen, in this same year, after a thorough study of the subject, concluded that tetanus antitoxin was of far greater value as a prophylactic than as a cure. He described the case of a sixty-year-old tanner who after a severe injury of the right forearm showed suppurative of the wound. In the secretions of this wound were found, by bacteriological examination, tetanus bacilli, and, accordingly, on the seventh day after injury he was given 100 units of tetanus antitoxin. No symptoms of tetanus developed at any time. Similar findings have been reported by Kolb and Laubenhaimer. However, such facts cannot be regarded as sure proofs

for the efficacy of antitoxin, as, among others, Bain has demonstrated the presence of tetanus bacilli in wounds where the disease did not develop and no antitoxin was given.

After tabulating the unfavorable results seen up to 1906 in the preventive treatment of tetanus, Bär stated that the most careful antiseptic treatment of complicated fractures into which dirt had entered was not able to render harmless the bacteria which might be buried in the wound, especially in those injuries produced by fragments of exploding shells where, because of the infected pieces burying themselves in the body, the danger of tetanus was more pronounced. He concluded from the reports of Herhold and Hohlbeck that, in the Russian-Japanese war, serum prophylaxis had been used with success.

A second article from Suter, in 1907, extensively considered all the phases of tetanus prevention. He stated that diligent search of the literature had failed to show a case where antitoxin had done harm, and disagreed with von Manteuffel, who thought that prophylaxis was impracticable in war. Suter admitted, however, that antitoxin in its present form might be difficult to use on the front—nevertheless, if given early enough, many deaths from tetanus might be prevented, a view shared by Munninger, who declared: "Preventive inoculation is, up to the present time, the best means of lowering the mortality of tetanus."

In the following year Le Deutu appeared as a strong partisan of prophylaxis, advising large and repeated doses of serum. He thought that every one of the 1200 deaths from tetanus occurring in the Franco-Prussian war of 1870 could have been prevented by antitoxin. Lucas-Championnière and also Vaillard defended the efficacy of preventive inoculation in spite of the increasing reports of failures following its use, especially in France.

Grazer, in 1910, recommended treating all wounds suspected of tetanus infection with the prophylactic injection of 20 to 100 units of antitoxin, and in the following year Remertz gave his opinion that this treatment would reduce the death rate of tetanus one-half, and that it should always be employed in wounds of both men and horses when such wounds were received in regions where tetanus was known to be prevalent. In this year also Biron and Pied confessed that, doubting its efficacy, they had not used prophylactic antitoxin from 1895 to 1902, and during that period had met with 11 cases of tetanus. From 1905 to 1910 the serum was used as routine treatment and no tetanus had appeared. Tizzoni, in 1912, introduced the theory that the blood of normal individuals to a certain extent would neutralize tetanus toxin, but with the help of antitoxin an enormous temporary increase in immunity could be obtained. For this reason he emphasized the value of prophylaxis, and recommended its use in surgical operations and after all shot wounds.

One of the most impressive series of facts in relation to the prevention of tetanus is associated with the annual Fourth of July celebration in the United States. For many years this holiday had been accompanied by an increasing number of both minor and major injuries, caused by blank cartridges, cannon crackers, toy pistols, etc. A considerable proportion of these injuries, nearly 10 per cent., were followed by tetanus, usually of a very virulent type. Thus in 1900, 500 deaths were said to have been due to tetanus, directly caused by wounds received during this celebration. Hence the *Journal of the American Medical Association* began in 1903 the collection of careful statistics and also at the same time conducted an extensive campaign both to discourage the use of toy pistols and similar injury producers and to encourage the treatment with tetanus antitoxin of all injured persons. The results of this campaign may be seen from the accompanying table, which shows that in 1904 the effect became first apparent, at which time a sudden drop occurred from 415 cases of tetanus (or 9.35 per cent.) of all injured persons in 1903 to 111 (or 2.52 per cent.) in the following year.

TABLE I.

Year.	Total injured.	Tetanus cases.	Per cent. of tetanus cases.	Deaths from tetanus.	Tetanus mortality. per cent.
1903	4449	415	9.35	406	97.8
1904	4169	111	2.52	87	78.4
1905	5176	104	2.01	87	84.0
1906	5466	89	1.45	75	84.0
1907	4413	73	1.65	62	84.0
1908	5623	76	1.35	55	72.1
1909	5307	150	2.82	125	83.2
1910	2923	72	2.46	67	93.0
1911	1603	18	1.12	10	55.5
1912	958	7	0.71	6	86.0
1913	1163	4	0.35	3	75.0
1914	1506	3	0.2	3	100.0

In respect to the use of antitoxin the *Journal* of that year (1904) gave the following comment: "The prophylactic treatment of all blank cartridge, giant cracker, and other similar wounds of the Fourth of July has been demonstrated to be positively successful many times before, but probably never on so large a scale as this year—having been employed in more cases than ever before. We have now records of upward of one thousand administrations of antitoxin in this way without a single untoward result of any importance and without a single case of tetanus developing. What motive can there be, therefore, in treating a Fourth of July injury without the prophylactic injection?" Individual reports have only added to the impressiveness of these statements. For example, in St. Louis, in 1903, according to Scherek, 56 cases of Fourth of July injuries occurred, from which 16 fatal cases of tetanus developed.

¹ Fourth of July injuries and tetanus, from statistics collected by Jour. Amer. Med. Assn.

In the three years following, 36, 84, and 170 such wounds, under prophylactic treatment, showed no case of tetanus. In the Harlem Hospital 100 cases of gunshot wounds were treated with antitoxin and no tetanus appeared. Luckett injected 60 of these injuries, each with 10 c.c. antitoxin, with the same success. However, one other case of his, a woman, who was treated with dry powdered antitoxin because she objected to the subcutaneous injection, later succumbed to a fatal attack of tetanus.

Nevertheless the judgment of the clinical world is not so unanimous as the foregoing might lead one to believe. In both France and Germany there is a consistent minority of physicians who point to the fact that ever since tetanus antitoxin has been used prophylactically there have appeared occasional cases of tetanus which have developed in spite of the treatment, *i. e.*, in a small but definite percentage of all cases so treated, the method had failed to give adequate protection. These failures have been especially numerous in Germany in the present war, and have led to a feeling of pessimistic skepticism in the minds of many doctors toward the use of tetanus antitoxin for any purpose whatsoever.

Accordingly it is proposed here to classify and analyze in two groups (1) the theoretical considerations and (2) the actual facts that underlie these cases, with the purpose of determining, if possible, the reasons for the failures and of establishing more firmly the principles which should govern the prophylactic administration of tetanus antitoxin. In group 1, as one of the most important of the theoretical considerations, may be mentioned the abnormal reactions exhibited by some individuals (1) toward certain diseases and (2) toward foreign serums. In the first class one finds those variations from the normal average which are well recognized in both men and animals. These individuals show such an extreme sensitiveness to certain toxins that the general rules for prevention and cure may prove entirely inadequate. So in tetanus the conditions for the growth of the bacillus may be so favorable, the absorption of the toxin so rapid and complete, and the sensitiveness of the vital centres to this toxin so exaggerated, that extraordinary and unexpected intoxication occurs in spite of the usual prophylactic and therapeutic measures. In the second class there is an abnormal reaction toward the serum itself. As far as can be determined the antitoxic property is added to the blood serum without appreciably affecting its physical or chemical constituents, and, aside from its ability to neutralize tetanus toxin, its fate in the body exactly corresponds to that of any other foreign serum injected under the same conditions. In other words the body endeavors to destroy or eliminate antitoxin just as it does plain horse serum. The elimination is accomplished by the glandular excretory organs, and the destruction supposedly by ferments usually newly formed in the body in response to the irritation of

the presence of this foreign proteid. We shall return to this subject in the discussion of anaphylaxis. Here it is sufficient to indicate the possibility that these ferments may be already present in the body at the time of the first injection in sufficient strength to destroy rapidly and render useless the antitoxic serum that is introduced. In this connection may be noted the fact that the second dose of antitoxin does not give so long a duration of protection as the first. (Behring.) The body has learned, *i. e.*, adapted itself, to destroy more rapidly and efficiently this injected serum. But if this ability by some chance were already possessed by the body cells and fluids before the first injection of the tetanus antitoxin (perhaps because of some previous serum injection), then such an injection might prove not only useless, but under certain circumstances, as will be shown, actually dangerous.

As the second factor in this first group may be considered the question of passive against active immunization. As yet no attempts have been made to provoke active immunity against tetanus in human beings. The dangers associated with tetanus toxin and the efficacy of early administration of tetanus antitoxin have not as yet justified the attempt to protect people against tetanus as against smallpox, typhoid fever, or cholera, *i. e.*, by vaccination. The advantages of active immunity, however, are clear. In the first place the protection is more enduring, usually lasting months or years instead of days, and in the second place, when infection occurs, "protection" is already present and able at once to neutralize the first toxin that may be produced. Also in active immunity foreign serums do not enter into consideration. The protective qualities are then a distinctive property of the body's own cells and fluids. If human serum could be used for antitoxin in human beings it would undoubtedly possess greater value both prophylactically and therapeutically. In fact, Wiedemann reported the case of a child suffering from traumatic tetanus in whom he used the serum obtained from 100 c.c. of the blood of a boy who had recovered from tetanus two years before. Ransom and Kitashima, in Behring's laboratory, found that goats' antitoxin given to other goats produced a passive immunization which was of nearly the same duration as the active immunization of the original goats. Naturally the extensive use of homologous serum in human beings is at present out of the question.

A further and important reason for the adoption of a rational and safe method of active immunization in tetanus is war. Wounded soldiers are notoriously liable to tetanus. The first treatments are often difficult, inadequate, and delayed. Were such soldiers previously actively immunized against tetanus as well as typhoid and cholera a percentage of deaths, always large enough to be disturbing and often extreme, would be almost entirely avoided and the trouble associated with ordinary prophylaxis would be unneces-

sary. Such protection is theoretically entirely possible. A practical and absolutely safe method is alone lacking. Manifestly the methods used at present in animals are not applicable to man, but I am convinced that the question deserves earnest consideration, especially in the light of the lessons learned from the present war. In this connection, Piorkowski has recently proposed the use of a preparation of heated dried cultures of tetanus bacilli which as a powder could confer immunity upon and also save mice when administered with or even later than inoculated garden earth.

The second main group of reasons for failures includes the study of individual cases and the actual circumstances under which failures in these cases have occurred. Accordingly in Table II have been collected and tabulated those cases which could be found in the literature in which prophylaxis failed to afford adequate protection. Similar cases which have occurred in the present war will be reserved for separate consideration.

The first and most important cause of these failures is undoubtedly the rapid formation and absorption of tetanus toxin following the injury. Kitasato inoculated the tails of mice with tetanus cultures and at varying intervals of time cut off the inoculated portions, thereby removing completely all further source of toxin production. He found that one hour after the inoculation such an operation was too late to save the animal from a fatal attack of tetanus. In close association with this fact is the extreme rapidity with which the absorbed toxin is bound to the nerve cells, where it cannot be neutralized. Donitz determined the amount of antitoxin necessary to neutralize a definite quantity of toxin when both were mixed *in vitro*. He then injected this amount of toxin into one ear vein of a series of rabbits, and at varying intervals injected antitoxin into the vein of the opposite ear. In four minutes it was necessary to use two times and in fifteen minutes twenty times the amount of antitoxin which had sufficed *in vitro*, and after one hour forty times this dose could barely save the life of the animal, while at the end of twenty-four hours an enormous increase (3600 doses) did not avail. Donitz concluded, among other things, that in cases of severe poisoning at least the lethal dose of toxin was already combined with the nerve structures at the end of four to eight minutes.²

Further evidence of this rapid binding power is presented by Hutehings, who infected the tails of sheep with tetanus cultures, and as soon as symptoms appeared cut off the infected portion. Tests of the blood at this time showed that 2 c.c. contained enough tetanus toxin to kill a 350-gram guinea-pig; 4500 units of anti-

² Another conclusion which was drawn by Donitz from these experiments was that "this combined toxin could be again separated from the nerve tissue, neutralized, and rendered harmless by the action of tetanus antitoxin." This conclusion has not been confirmed.

TABLE II.—Showing published cases in which prophylactic applications of tetanus antitoxin failed to prevent tetanus. 0 = recovery; + = death.

No.	Author.	Age.	Interval between injury and injection.	Quantity of serum.	Incubation time, days.	Result.	Remarks.
1	Buschke	?	6 days	5 c.c.	11	1	Author himself doubtful over diagnosis; antitoxin late.
2	Tizzoni	?	4 days	4 gm.	4	0	Antitoxin late.
3	Tizzoni	?	24 hours	?	12	0	Tizzoni serum.
4	Remy	49	Same day	10 c.c.	42	+	"Delayed tetanus."
5	Reclus	25	Same day	7 c.c.	12	+	Intracerebral antitoxin; French serum.
6	Bougle-Reynier	48	Same day	10 c.c.	15	0	"Prolonged incubation."
7	Peyrut	?	?	?	12	+	Details wanting.
8	Haltenhoff	3	2½ days	10 c.c.	4½	0	Antitoxin too late; diagnosis in doubt.
9	Ulrich	43	3 days	?	7½	0	Delayed tetanus.
10	Maunoury	30	Same day	10 c.c.	26	+	Delayed tetanus.
11	Mauclair	?	1 day	10 c.c.	17	0	Prolonged incubation.
12	Krafft	31	6½ hours	10 c.c.	0½	+	Antitoxin too late; intracerebral injections.
13	Vidal	7	1½ hours	15 c.c.	3	+	French serum.
14	Grenda	?	Same day	10 c.c.	5	+	Swiss serum.
15	Lampelougue	?	3 days	10 c.c.	59	+	Delayed tetanus.
16	Tixier	?	5 days	10 c.c.	8	+	Antitoxin too late.
17	Terrier	57	Same day	10 c.c.	87	0	Delayed tetanus.
18	du Sejour	60	1 day	10 c.c.	23	+	Prolonged incubation.
19	Ruter	30	Same day	10 c.c.	47	0	Delayed tetanus.
20	Küster	36	2½ hours	40 A. F.	7	0	German serum.
21	Pochhammer	32	14 hours	20 A. E.	14	+	Antitoxin late; German antitoxin.
22	Kocher	?	?	10 c.c.	21	0	Prolonged incubation.
23	Lotheissen	46	2 days	100 A. E.	6	0	Antitoxin too late.
24	Lop	?	1 hour	?	7	+	Powdered antitoxin.
25	Ochsner	?	16 hours	10 c.c.	12	0	Antitoxin late; French serum.
26	Bell, J.	9	1 day	5 c.c.	47	+	Delayed tetanus.
27	Freeman	?	Same day	10 c.c.	6	0	American serum.
28	McArthur	?	Same day	10 c.c.	14	0	Fractured skull; American serum.
29	Tyson	48	4 days	30 c.c.	12	0	Antitoxin late.
30	Brawn	14	3 days	10 c.c.	4	0	Antitoxin late.
31	Bär	13½	3½ hours	10 c.c.	8	0	Swiss serum.
32	Ellbogen	7	1 day	20 c.c.	18	0	Prolonged incubation.
33	Reynier	20	Same day	10 c.c.	11	0	French serum.
34	Thiery	?	?	10 c.c.	8	+	Essential details lacking.
35	Senechal	26	6 hours	10 c.c.	8	0	French serum.
36	Mauclair	34	Same day	?	6	+	French serum.
37	Terrier et Mercedé	18	Same day	10 c.c.	6	+	French serum.
38	Mignard	7	4 hours	?	4	+	French serum.
39	Lang	?	2 days	10 c.c.	11	0	Antitoxin late.
40	Lang	3½	4 hours	10 c.c.	12	+	Swiss serum.
41	Lang	9	2 days	100 A. E.	4	+	Antitoxin late.
42	Luckett	?	?	?	4	+	Powdered antitoxin.
43	Roger	?	?	?	5	+	Powdered antitoxin.
44	Roger	?	?	?	5	+	Powdered antitoxin.
45	Monod et Vanvrie	52	Same day	10 c.c.	75	0	Delayed tetanus.
46	Viscontini	40	?	10 c.c.	9	+	Essential details lacking.
47	Vennat et Michelean	?	1 day	10 c.c.	14	+	Diagnosis doubtful.
48	Vennet et Michelean	?	?	10 c.c.	?	0	Diagnosis doubtful.
49	Tuffier	7	3 hours	?	6	+	French serum.
50	Reynier	7	Same day	?	5	+	Powdered antitoxin.
51	Reynier	7	Same day	?	8	+	Powdered antitoxin.
52	Reynier	7	3 hours	?	7	+	Details insufficient.
53	Masse	7	?	?	51	?	Delayed tetanus.
54	d'Hotel	7	Same day	10 c.c.	16	0	Prolonged incubation.
55	van Haver	19	3 hours	20 c.c.	11	+	Swiss serum.
56	Simon	5	Same day	20 A. E.	1	0	Diagnosis doubtful.
57	Schlatter-Bär	20	3 hours	10 c.c.	23	+	Prolonged incubation.
58	Bär	5	Same day	10 c.c.	21	0	Prolonged incubation.
59	Viscontini	40	?	10 c.c.	10	+	Essential details lacking.
60	Rowan	37	5 hours	1500 units	26	+	Delayed tetanus.
61	Delbet	?	?	?	3 or 4	0	Essential details lacking.
62	Arrou	13	Second day	10 c.c.	8	+	Antitoxin late.
63	Hulser	7	?	10 c.c.	6	+	Diagnosis doubtful.
64	Riclé	9	10 hours	10 c.c.	8	0	French serum.
65	Potherat	28	Second day	10 c.c.	4	+	Antitoxin late.
66	Ritter	?	?	?	?	+	Insufficient details.

toxin² was then injected, and twenty-four hours later a test of the blood showed no toxin present. However, in spite of daily injections of 4500 units the sheep invariably died. Neither the symptoms nor the course of the disease were influenced by these injections.

Many facts lead one to believe that in man we have to deal with nerve structures extremely sensitive to tetanus toxin. Some of the clearest evidence having a bearing on this point occurred in an outbreak of tetanus in St. Louis following the administration of diphtheria antitoxin. Investigation showed that a certain supply of this antitoxin had, in some unknown manner, become contaminated by tetanus toxin (not tetanus spores). A comparison of the amounts of this fluid which had produced accidental death in human beings and the amount found necessary to kill a 300-gram guinea-pig demonstrated that the susceptibility of the two was nearly the same, *e. g.*, 0.1 c.c. would kill a 300-gram guinea-pig, and 10 c.c. was sufficient to produce fatal tetanus in a child weighing fifty pounds. Also the occurrence of symptoms of undoubted tetanus only three and four days—in fact even two days—after the injury indicates the exceeding rapidity with which all these processes may take place.

The second cause for failure in these cases is supplementary to the first and rests in the slowness with which antitoxin is absorbed into the blood stream. In a series of careful experiments Knorr found that in animals subcutaneous antitoxin did not attain its maximum in the blood stream until twenty-four to forty hours had elapsed after the injections. Naturally this time may vary within wide limits, depending upon special conditions. For example, tissues of the young absorb more rapidly than those of the old, the muscles better than the subcutaneous fascias, and these in turn better than the skin. Finally, inflammation, shock, vascular spasm, congestion, heart weakness, etc., all tend to decrease the rate at which antitoxin enters the blood stream. While many of these factors may also operate to decrease the rate of absorption of the toxin it must be remembered that toxin is by its nature readily absorbable, while antitoxin, on the contrary, perhaps because of the larger size of its molecule, is naturally slowly absorbable. From the foregoing it becomes clear that, given a case where toxin is formed and absorbed with unusual rapidity and the antitoxin is injected too late or for some other reasons is absorbed too slowly to neutralize this toxin, harmful and even fatal consequences may readily follow. That such a set of circumstances may occur can be plainly seen from the statistics presented in Table II. The time of giving the antitoxin varied from a few hours to as late

² The United States antitoxin unit represents that amount of antitoxin which can save the life of a 350-gram guinea-pig for ninety-six hours when the animal has also received 100 times the minimal lethal dose of a test toxin preserved in the laboratory of the United States Public Health and Marine Hospital Service.

as six days after the injury. Under certain circumstances, as has been demonstrated, a few hours' difference in time might represent the difference between a non-fatal and a fatal intoxication.

The third cause for failures which appears in this table is the short duration of the immunity conferred by injections of antitoxin. Behring stated that the first dose of antitoxin gave an immunity lasting twenty days and that a second injection at the end of this time would add only a further protection of from five to eight days, *i. e.*, repeating the injection diminished the duration of the protective action to five to eight days. According to Tizzoni, antitoxin protects for fourteen days; Delbet estimated the duration at ten days, while Glasser suggested a repetition at the end of eight days and Vaillard declared that the serum ceased to be effective after a week or at the very longest at the end of two weeks. Ruediger in guinea-pigs found that passive immunity against tetanus produced by moderate doses of tetanus antitoxin lasted a little less than three weeks, and that the immunity conferred by larger doses continued only a few days longer. This subject was considered worthy of further experimental proof, and, accordingly, through the kindness of the attending physicians in the Freiburg military hospitals, especially of Prof. Kähler and Dr. Weidenmüller, samples of blood from various patients who had been given prophylactic injections of twenty antitoxin units (German standard) were tested for their antitoxin content.

In these experiments 1 c.c. of the blood serum from these samples was mixed with two or three times the minimal lethal dose of tetanus toxin, and this mixture was injected into the hind leg of rats. The rats varied in weight from 100 to 200 grams and the dose necessary to kill the larger rats was used as the minimal lethal dose. In every case controls were injected with the toxin alone. Other controls were injected with normal blood alone and others with normal blood plus twice the usual minimal lethal dose of toxin. The blood serum alone proved to be non-toxic and neither did it possess any appreciable antitoxic properties. In this particular I was unable to confirm Tizzoni's assertion that the blood of normal persons would neutralize tetanus toxin. In all seventeen samples of human blood were tested. These were removed at intervals of from three to twenty days after the antitoxin injection. All the samples representing a duration below fifteen days held sufficient antitoxin to protect fully the injected animals. Of those taken on the fifteenth day from five samples tested, one rat died from tetanus, the death, however, being delayed three days beyond that of the control. That the other fifteen-day samples held only a diminished amount of antitoxin was shown when after injecting one sample from which only 0.5 c.c. of serum could be obtained death occurred, and in another where the toxin was repeated without

the serum the animal died two days after the control. In a twenty-day sample the rat died one and a half days later than the rat injected with toxin alone. These facts permit the conclusion that passive immunity in man conferred by twenty units of antitoxin is effective for about twelve days and contains some protective powers for eight to ten days longer.

Hence, given a case in which prophylactic antitoxin is administered and for one reason or another the tetanus toxin is not formed or possibly not absorbed until after twelve to fifteen days have passed we may expect very little protection from the antitoxin first given and at the end of twenty-five days absolutely no protection at all.

Consulting again Table II, one finds that in 10 cases from twenty-six to eighty-seven days passed between the last injection of tetanus antitoxin and the first symptoms of tetanus, which here represent examples of what I have called delayed tetanus, and in 8 other cases from fifteen to twenty-three days elapsed (examples of prolonged incubation⁴). In the first group 5 cases died, 4 recovered, and the outcome of 1 is unknown; while in the second group only 2 died and 6 recovered, suggesting that in the latter group the protective effects of the serum had not entirely disappeared.

Examples of a long incubation time in tetanus (delayed tetanus) are of frequent occurrence in the literature, and the possibility of a tetanus infection lying dormant in the body and only developing when favorable circumstances present themselves has been shown in animal experiments. For example, Vaillard and Rouget described instances where guinea-pigs were inoculated with tetanus spores plus lactic acid, and did not develop tetanus until more than four months had elapsed. Such cases of delayed tetanus, as well as those of unduly prolonged incubation, present a problem in both the prophylaxis and the treatment of tetanus which has not yet been satisfactorily solved. Repetitions of the antitoxic serum are not always practical, and, moreover, the succeeding doses always afford an ever-diminishing period of protection. Here, again, the production of active immunity would be of decided advantage.

As the fourth cause for failures may be considered the method of application of the antitoxin, Calmette's recommendation that dry powdered antitoxin be applied locally to the wound led to its widespread use not only in France but also in other parts of Europe and in America. Practically the method has many obvious advantages; theoretically, however, it is not based on logical grounds. First it does not, as a rule, reach the tetanus inciter, the bacilli being buried deep in the tissues. Experience has again and again demonstrated that local disinfection and cleansing are not able to prevent tetanus. Hence for the efficacy of the powder we are largely

⁴ The limits for this latter class have been arbitrarily placed at between fifteen and twenty-five days.

dependent on its solution and absorption by the body juices. Under the circumstances not only is this absorption slower than with the fluid antitoxin but manifestly less dependable. Letulle's enthusiasm for its use on the umbilical cords of newborn children may be explained by the fact that in infants absorption by the tissues is extremely rapid, and a fresh wound without inflammatory reaction is much more suited for these applications than a wound filled with blood clots and inflammatory débris, such as is usually presented in adults. Clinical opinions, however, have varied widely. Delbet believed the convenience of the powder was its only recommendation, and that in most cases it was useless. Remertz concluded: "Das bestreuen der Wunde mit Antitoxin in Pulverform ist als nutzlos zu verwerfen." Examination of the cases in Table II tends to confirm this last view. Six cases were treated prophylactically by powdered antitoxin and all six ended in fatal tetanus.

Yet a successful method of local application of antitoxin is demanded. In the well-ordered hospital or physician's office the subcutaneous or even the intravenous injections of antitoxin offer little difficulty. On the other hand, in injured persons far removed from either of these places, especially in those wounded in war, such injections may be very difficult, and while eventually an injured soldier can obtain an injection of antitoxin, in the meantime valuable time may have been lost and a fatal case of tetanus may have been permitted to develop because the antitoxin could not be early enough administered.

Various solutions of this problem have been offered. As early as 1900 Behring stated that experiments on animals had demonstrated the importance of the direct contact of tetanus antitoxin with the infected and toxin-containing tissues, and laid great stress on the advantages of direct application to the point of infection and its vicinity. The results given above show, however, the futility of powder. Behring's general suggestion was applied more successfully by Suter, who soaked tampons with antitoxin and bound these directly to the wound. Bockenheimer proposed mixing antitoxin with salve. Among others, Graser reported good success with the tampons but was unable to obtain results with the salve. Bockenheimer himself did not present convincing proof of the efficacy of this method. His advocacy of the salve was based on the principle that fatty substances possess a certain neutralizing property against tetanus toxin, a fact which led him to recommend, for example, Peruvian balsam salve with or without antitoxin. He also admitted that antitoxin mixed with salves rapidly lost its power to neutralize toxin, and therefore had always to be made freshly. I attempted to immunize rats with a mixture of antitoxin and lanolin by thoroughly rubbing this on the skin. In two separate sets of experiments the treated rats died at the same time as the controls.

Suter's proposal to use liquid antitoxin has this advantage over the powder, namely, it does not need to be first dissolved and therefore more readily penetrates to the deeper tissues of the wound and more quickly mixes with the wound fluids, not only thereby destroying local toxin but also furnishing general protection by absorption into the blood. In my experiments wounds were made in the skin and muscles of the backs of laboratory animals and antitoxin-soaked tampons were bound onto the wounds. Twenty-four hours later the animals were given three times the minimal lethal dose of tetanus toxin and showed no symptoms of tetanus at any time.

This method, however, is wasteful and involves the use of bottles of fluid antitoxin which are not only liable to breakage but also to spontaneous deterioration of the antitoxic properties of the serum. Consequently an attempt was made to combine the advantages of Calmette's method with those of Suter's. Liquid antitoxin was poured on pads of sterile absorbent cotton in such amounts as to render the cotton uniformly moist but not wet enough to drip. These pads were then dried for twenty-four hours in a moderate heat (40° to 45° C.). A previously sterilized evaporating dish or earthenware mortar covered with a double layer of filter paper was found satisfactory as a container. Drying in vacuum did not appear to offer any advantages. The dried antitoxin cotton became a stiffened mass, resembling dried paper pulp. This was weighed and then divided into pieces which by weight would represent definite quantities of antitoxin, *e. g.*, if the entire mass contained twenty units of dried antitoxin, one-twentieth by weight would represent one unit. Pieces of this prepared cotton, representing amounts varying from one to two and a half units of antitoxin were then bound on freshly made wounds of rats. The results were not entirely satisfactory. If fresh serum or blood were present in the wound and the dry cotton could be bound closely to the wound, varying degrees of protection were afforded; but more often from lack of fluids no solution of the antitoxin took place and hence no absorption. This latter fact was demonstrated by the following occurrence: The dried cotton was removed from a rat which had succumbed to tetanus in spite of its presence, and after moistening this cotton it was applied to a fresh wound in another rat. A three-times minimal lethal dose of tetanus toxin injected on the following day failed to produce tetanus and the rat remained alive.

This led me to adopt the method of simply keeping the prepared cotton in a sterile container and, when it was required for use, to moisten it with physiological salt solution, distilled water, sterile bouillon, or any clean fluid which might be at hand. To test its efficacy on natural tetanus infections, 10 mice were inoculated with garden earth which in previous experiments had produced tetanus in mice with 100 per cent. mortality; 5 mice received, at the same time with the earth, fragments of dried antitoxin cotton

which had been moistened directly before application to the wound. The other 5 mice, serving as controls, were inoculated with the earth alone and all died from typical tetanus in the course of three days. Of the 5 treated mice 1 only, which had early torn the cotton dressing from the wound, showed any sign of tetanus, and even then it lived for eight days, evidently having received some protection, as it lived five days beyond the controls. The remaining four at no time showed any sign of tetanus. Portions of the prepared cotton tampons were used after they had been kept six weeks, and with these pieces the lives of rats were protected against a three-times minimal lethal dose of tetanus toxin. All the rats treated in this manner have received protection. Each time the cotton was moistened immediately before application to the wound. In two animals which had torn the tampon away shortly after the operation a local tetanus developed, but the rats lived and the local symptoms gradually disappeared.

In this method I believe that the advantages of the powdered antitoxin of Calmette and of the fresh antitoxin tampons of Suter have been retained and the disadvantages removed. I do not wish to be understood as recommending this method as a substitute for the subcutaneous or intravenous injections of fresh potent antitoxin. Where, however, such injections are impracticable these dried antitoxin tampons which hold their efficacy at least six weeks (and probably longer) can be carried with the first aid dressings and can be moistened and immediately bound on the wound by the doctor or the injured person himself.

Still another application of these tampons is possible: When for one reason or another a repetition of the serum becomes desirable, if the wound be still unhealed they can be used for this repetition and thus all fear of dangerous anaphylaxis can be avoided. The absorption is slower, but the effects are also for that reason of slightly longer duration. The lack of danger, the absence of wastefulness, the certain, even if slower, action, and, above all, the ease of application even by the laity are points which favor a thorough trial of these antitoxin tampons.

In conference with the Höchst Farbwerke² over this method, they stated that their antitoxin was combined with a certain percentage of glycerin which might interfere with both its drying and preservation. They indicated, further, that a special preparation could be made to meet a demand for such a product.

Further, I have experimentally tested other possible routes of absorption, *e. g.*, through the peritoneal and the pleural cavities, and have not found any advantage over the subcutaneous injections. An attempt was made to confer immunity on guinea-pigs

² At this point I wish to express my sincere gratitude to the Höchst Farbwerke, who supplied both the antitoxin and the tetanus toxin used in these series of experiments.

by placing tetanus antitoxin-soaked tampons in the nostrils, but these experiments were entirely unsuccessful.

Returning to the list of failures, as a fifth possible cause may be suggested active surgical interference in the wound. It is an experience which has been repeated several times in cases which have remained for days, weeks, and even months free from any symptoms of tetanus that a severe and even fatal attack of the disease may occur suddenly after some surgical interference, such as amputation, vigorous cleansing, opening abscess pockets, etc. Many of the cases are examples of delayed tetanus. It is difficult to know exactly what occurs under such circumstances. I can only suggest the possibility that such surgical measures either break up surrounding protecting zones of granulation tissue and promote a fresh absorption of tetanus toxin or provide new and better conditions for the development of the tetanus spores lying dormant in the wound. If surgical interference is necessary the antitoxic serum in some form should be repeated before the operation. In cases of this kind, as previously suggested, the dried antitoxin tampons could be used to advantage.

As a sixth possible ground for failure may be mentioned the character of the antitoxin used. It is rather remarkable that of the 66 failures in Table II, 35, or more than one-half, were treated with French antitoxin. Of this number 24 died, which is two-thirds of the total number of deaths (36) tabulated. Here it is of interest to note the report made by Anderson of the United States Public Health Bureau in 1910. He tested the various tetanus antitoxins which were then on the market, and his results showed that while the United States serums varied from 77 units (United States standard) per 1 c.c. for one sample to 769 units for another and the Höchst serum contained 333 units; on the other hand, two samples from the Pasteur Institute and one from another French institute all contained less than 50 units in each cubic centimeter.

Turning now to the tabulated list of failures a more critical analysis can be made. In 6 of the cases (24, 42, 43, 44, 50, 51) the use of powdered antitoxin may well be the cause of non-success. In 10 more (4, 9, 10, 15, 17, 19, 26, 45, 53, 60) one finds excellent examples of delayed tetanus, 8 others (6, 11, 18, 22, 32, 54, 57, 58) show abnormally prolonged incubation periods. Essential details fail in 7 cases (7, 34, 46, 52, 59, 61, 66) and in 4 more (47, 48, 56, 63) the diagnosis is gravely open to question. Of those that remain, if one should judge arbitrarily that after twenty-four hours the antitoxin was probably administered too late, one can exclude 12 further cases (1, 2, 8, 12, 16, 23, 29, 30, 39, 41, 62, 65). Of the 19 cases which remain 1 (3) was treated with Tizzoni's antitoxin, 4 (14, 31, 40, 55) received Swiss serum, 2 (20, 21) German, 2 (27, 28) American, the remaining 10 (5, 13, 25, 33, 35, 36, 37, 38, 49, 64) were all inoculated with French antitoxin. Of the 19 cases 10 died, a mortality of 52 per cent.

Further analysis of these 19 cases does not offer much added value. It is not my aim to "explain away" all cases of failure in the prophylactic treatment of tetanus, for, as has been intimated, it is clear that in the inherent character of the method itself lies always the possibility that failure may enter at any time. I have simply endeavored to show that when the principles which should govern the use of tetanus antitoxin are closely followed not only is the percentage of cases resulting in spite of prophylaxis a very small one, but also as we become more skilful in the preparation of these serums and more rational in the treatment of "tetanus suspicions" wounds, even this percentage may be expected to diminish.

TETANUS PROPHYLAXIS IN THE PRESENT WAR. As would be expected the experiences with tetanus in this war are almost as variable and opinions as contrary as have been already noted in private clinical practice. When at the end of the war a complete summary can be made of all the facts concerning tetanus we may look for much valuable data over both preventive and therapeutic treatments. At present most of the statistical evidence is of a much too fragmentary nature to furnish a basis for final judgment.

The first account of tetanus from the prophylactic side was given by Hufnagle in the conference of army surgeons in Namur, November, 1914, at which time he reported that among 2193 wounded treated in the "Festungslazarett" of Namur from September 11 to November 30 there developed 27 cases of tetanus. Beginning the middle of October, all wounded soldiers received a prophylactic injection of twenty units of tetanus antitoxin, and since that time no further cases of tetanus had appeared, although among the 1195 wounded who were treated in the hospital since that date were many who had received very serious wounds.

The results of a collective investigation made by Madelung are of particular interest, especially in relation to prophylaxis. In thirty-seven hospitals where no prophylactic injections were given among 8145 wounded, 63 cases of tetanus developed, a percentage of 7.7. In one hospital where prophylaxis was administered in selected cases from 19,432 wounded occurred 107 cases, or 5.5 per cent. In three other hospitals where protective injections were the routine treatment, among 2104 wounded only 12, or 0.57 per cent. developed tetanus, a striking illustration of the efficacy of antitetanic serum in preventing tetanus when used systematically. From the total number treated only 20 developed tetanus in spite of preventive injections, which in no case were made on the same day that the wound was received, and in half of the cases injections were not given until six days had elapsed.

Walter observed in a hospital in Paris among 270 wounded German prisoners 19 cases of tetanus, and he emphasized the coincidence that all of these wounds were received in the same region near the

Marne. Prophylaxis in those having severe wounds was attempted in the ambulance of the second help line, or at the latest in the hospital, and at the time of his report had given very good success.

Goldscheider declared himself in favor of protective inoculations and gave the results of prophylactic treatment on his service from the beginning of the war until October 1. Among 500 wounded who had been given a prophylactic injection of twenty units of antitoxin, 4, all of whom had shown prodromal symptoms before the injection, alone developed tetanus, but no further cases were seen.

All dirty wounds were treated by Gasch with protective serum, and among 700 of such no tetanus appeared. One soldier, slightly wounded on the toe, who was not injected, developed a fatal case of tetanus.

Sieur, before the French Académie de Médecine in the early part of 1915, stated that although in 1907 certain physicians had not hesitated to doubt the efficacy of prophylaxis, attributing the constant decrease in tetanus to the use of antiseptics on the wounds, he himself credits the absence of it among soldiers of his ambulance corps to the use of prophylactic doses of serum, systematically given and renewed at regular intervals. Among 17,507 wounded only 7 cases of tetanus occurred, in which the first symptoms appeared between twenty-four and sixty hours after. In not one of these cases had prophylactic antitoxin been given.

Behring in a review of the subject emphasized again many of the facts to which he had frequently before drawn attention. Quoting from Dreyfus, he stated that in the Spanish-American war tetanus was completely abolished after the protective injections had been instituted.

One might continue to add further opinions for and against prophylactic treatment of those wounded in war, but the above illustrates sufficiently the views held at this time. It must always be kept in mind that injuries caused by shrapnel, bursting shells, and deeply penetrating bullets are, from the stand-point of tetanus, the most dangerous of all wounds. They are usually deep, contain fragments of clothing, pieces of bone, dirt, or other foreign bodies, and because of their situation demand an expectant rather than a radical treatment. The immediate care of these wounds under the circumstances is not always possible, and shock, loss of blood, and exhaustion all play a part in lowering resistance and causing a condition particularly susceptible to dangerous infections. Antitoxin may be delayed in administration and slow in absorption, while, on the other hand, in a few hours the tetanus spores buried deep in the tissues in the presence of blood clot and other débris have abundant opportunity to multiply rapidly and in many cases toxin production is undoubtedly well advanced at the end of twenty-four hours.

ANAPHYLAXIS. One further point deserves consideration in the discussion of tetanus prophylaxis, and that is the so-called anaphylactic reactions. Following the use of diphtheria antitoxin as a therapeutic agent, innumerable instances of urticarial eruptions, occasional serious attacks of acute intoxication, and rarely even cases of sudden death were reported. The same has been true, although to a far less extent, after the use of tetanus antitoxin. Lapiere collected the cases of what he was pleased to denote "accidents dus à la sérothérapie antitétanique." In this collection appear all manner of complications which, because they were preceded by an injection of tetanus antitoxin, were judged by the *post hoc, propter hoc* standard and grouped together as results of the injections. The fact that in the administration of any foreign serum there is a certain possibility of more or less serious intoxication should cause one to exercise the utmost care in attributing to these injections only the consequences which rightly belong to them.

I have previously indicated what occurs when this foreign serum is introduced into the body. Destructive and excretory processes begin at once and continue as long as the serum, as such, remains in the body. But the absorption and excretion are uncommonly slow, owing to the peculiar nature of the substance, and consequently the process of destruction plays an important role. Exactly what this is has not yet been fully explained, but many facts point to the hypothesis that a ferment-like activity operates to split the proteid of the serum into less complex and more readily disposable compounds. Some of these compounds are undoubtedly poisonous for the body. When a guinea-pig receives an injection of horse serum or any alien soluble proteid and, after an interval of ten to twelve days, a second injection of the same substance, violent and even fatal symptoms of intoxication are liable to ensue. This is, of course, the well-known phenomenon of anaphylaxis, and under certain circumstances can occur in human beings following the injection of antitoxin, which is generally a modified horse serum. Probably 50 per cent. of the cases in which this serum is injected show some slight manifestations of this phenomenon.

Most frequently this consists of an erythematous or even a papular urticarial-like itching eruption which develops from forty-eight hours to seven days after the injection, and lasts about thirty-six hours. It may be accompanied by slight fever, headache, malaise, and vague pains in the back and joints. All varying intervening stages may be seen, and the almost invariable rule is rapid and complete recovery. Very occasionally the symptoms are more threatening and simulate those of an acute exanthematous disease with, however, a much shorter course and generally with no disastrous consequences. Still more rarely may be seen the exceptional case in which sudden and overwhelming intoxication occurs, and death

may take place a few minutes after the injection. Such a case in which death occurred within five minutes after a prophylactic injection of tetanus antitoxin was the subject of a medicolegal investigation in the state of Minnesota. Another similar case is reported by Riche in 1912: A girl, aged eight years, after an injury of the hand, was given 10 c.c. of antitetanic serum. A few hours later symptoms of collapse ensued and she died without in any way responding to stimulants.

That such occasional accidents should have no bearing on the use of diphtheria or tetanus antitoxin hardly needs to be argued. The fact that in the use of antitetanic serum serious consequences are extremely rare and with the purification of the antitoxin are becoming increasingly rarer is a hopeful sign that even this disadvantage may finally be entirely overcome. By carelessly ascribing to antitoxin injections all sorts of unreasonable and often absurd consequences, much harm may be done not only among the laity, but also among the medical profession. For example, in Lapierre's collection is a case reported by Cumus where death, undoubtedly caused by osteomyelitis and sepsis, was credited to antitoxin which had been injected three days before!

CONCLUSIONS. 1. The most ideal and perfect protection against tetanus is the protection of active immunity produced before the infection has occurred. This admittedly is not yet practical, but deserves further consideration and research.

2. In the large majority of cases the subcutaneous injection of twenty units immediately after the injury will prevent with certainty the occurrence of tetanus. The delay of a few hours in making the injection may mean the loss of life.

3. Local applications of fluid antitoxin on the wound are efficacious but unnecessarily wasteful and not always practical.

4. In cases where injections cannot readily be made, especially in time of war, the immediate application to the wound of dried antitoxin tampons moistened by clean fluid may be used as a temporary substitute until fluid antitoxin can be injected.

5. Powdered antitoxin on the wound is not, as a rule, dependable. Its one useful field is perhaps the prevention of tetanus neonatorum.

6. Certain failures are to be expected in the prophylactic treatment of tetanus as carried out at the present time. Occasional cases of tetanus will develop in spite of the most careful precautions.

7. The protection afforded by antitoxin lasts from two to three weeks. Hence in cases of protracted suppuration or where for other reasons secondary surgical interference is contemplated either second injections of antitoxin should be made or dried antitoxin tampons freshly moistened should be placed on the wound.

8. Certain complications, most frequently urticarial-like eruptions, and very rarely more serious results may follow injections of antitoxin.

Finally, I wish to emphasize once more that we are not dealing with an ideal remedy. There are few if any such known to man. Hence one must frankly face and admit its disadvantages. At the same time neither hasty clinical opinions based on empiricism nor narrow-visioned laboratory theories can alone guide one's judgment. A calm recognition of all the facts, the disadvantages and the advantages, and the reasons for both will surely lead to an eventual proper line of action based, as it always should be, on the broad foundation of reason and experience.

It gives me pleasure here to express my sincere thanks for the inspiration, counsel, and uniform kindness of Prof. L. Aschoff, in whose laboratory this work was done.

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